Cardiovascular risk factors in Aortic Stenosis

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Akademisk avhandling

som med vederbörligt tillstånd av Rektor vid Umeå universitet för avläggande av medicine doktorsexamen framläggs till offentligt försvar i Sal B, NUS 1D-Tandläkarhögskolan, fredagen den 23 februari, kl. 13:00. Avhandlingen kommer att försvaras på svenska.

Fakultetsopponent: Professor Peter Nilsson, Institutionen för kliniska vetenskaper, Lunds universitet, Lund, Sverige.
Aortic stenosis (AS) is the most common hemodynamic significant valvular heart disease and affects about 2% of the population. The incidence increases with age. When symptoms of the stenotic aortic valve disease eventually occur the 2-year mortality exceeds 50%. Aortic valve replacement (AVR) by surgery or by catheter intervention is the only known treatment. The causes of AS are only partly known, despite that the disease has been known since the beginning of 17th century. In younger individuals, a bicuspid valve is present in about 80% of the cases. The traditional cardiovascular risk-factors for ischemic heart disease have been linked to AS, and the histology of the stenotic aortic valve and the atherosclerotic plaques shares several features such as inflammation, lipid deposition and calcification. High levels of the lipoprotein Lp(a) has been linked to both atherosclerosis and AS, and a causal relation with AS is supported by Mendelian randomisation. End-stage renal disease is associated with increased risk of AS but if early impairment increases the risk is not known.

Material and methods: We identified 799 patients with surgery for valvular heart disease and/or disease of the ascending aorta with a prior participation in one of three large population based health surveys in northern Sweden (Västerbotten Intervention Program [VIP], MONItoring Of trends and Determinants in Cardiovascular Disease survey [MONICA], and the Mammary Screening Project [MSP]). For each case, four referents matched by age, gender, type and date of surgery, and geographical area were randomly selected. From the health surveys, data on cardiovascular risk-factors and health history as well as measurements of anthropometry, blood pressure, glucose and cholesterol levels were retrieved. Each case was carefully validated and data from pre- and perioperative assessments were collected. The presence of coronary artery disease (CAD) was determined from the preoperative coronary angiogram. Apolipoproteins B and A1, Lp(a), creatinine and cystatin C were analysed in samples obtained at the initial survey. As this is a matched case-referent study where cases and referents had the same follow-up duration within strata, logistic regression using the conditional maximum likelihood routine designed for matched analysis was used to estimate odds ratios (ORs) with 95% confidence intervals. Studied variables were tested in uni- and multivariable models.

Results: Paper 1: Of the identified 799 cases with questionnaires, 322 were primarily operated for AS, 91 for aortic regurgitation, 181 for mitral regurgitation, 131 for disease of ascending aorta, 52 for CAD (and concomitant valvular or aortic disease). The remaining 22 had various indications for valvular heart surgery and were excluded. Altogether 38% of patients were women. Aortic stenosis: Hypertension (OR 1.87 [1.37–2.54]), diabetes (OR 1.78 [1.01–3.11]) and total cholesterol (OR 1.64 [1.07–2.49]) were associated with future AVR. After exclusion of concomitant CAD, none of the these risk-factors remained significant. Aortic regurgitation: None of the cardiovascular risk-factors was associated with increased risk for aortic regurgitation demanding surgery, whereas high levels of cholesterol were associated with reduced risk for surgery (OR 0.29 [0.12–0.71]). Mitral regurgitation: High levels of cholesterol associated with surgery for mitral regurgitation (OR 1.74 [1.01–3.00]), but not in those without CAD. Disease of the ascending aorta: Hypertension (OR 2.42 [1.44–4.06]) and previous smoking (OR 1.97 [1.12–3.49]) related to increased risk for surgery of the ascending aorta, whereas diabetes was inversely associated with surgery (OR 0.09 [0.01–0.73]). Excluding CAD, only diabetes remained protective (OR 0.24 [0.07–0.81]). Paper 2: 322 patients underwent AVR, and 70 had surgery before the age of 60 years and 252 had surgery after 60 years of age. After exclusion of patients with CAD, 49 and 82 patients remained in these age groups. Arterial hypertension associated with future AVR in those operated before the age of 60 years regardless of concomitant CAD or not (OR 3.40 [1.45–7.93]) and OR 5.88 [1.46–23.72]). In those older than 60 years at surgery and with concomitant CAD, all traditional cardiovascular risk factors associated with surgery, but in those without concomitant CAD, only impaired fasting glucose (IFG) was associated with surgery (OR 3.22 [1.19–8.76]). Paper 3: 336 patients having surgery for AS. Lipoprotein(a) (Lp[a]) was independently associated with surgery in those with concomitant CAD (OR 1.29 [1.07–1.55]), but not in those without CAD. A high Apo B/A1 ratio was associated with surgery in patients with CAD (OR 1.43 [1.16–1.76]), but not in those without. Paper 4: The same cohort as in paper 3 was examined. Renal function was estimated by the ratio between glomerular filtration rate (eGFR) obtained from cystatin C and creatinine, and a low ratio indicates early impairment of renal function (“shrunken pore syndrome”). A high ratio independently associated with lower risk for future AVR (OR 0.84 [0.73–0.97]). Protective effect was seen in women but not in men (0.74 [0.60–0.92] and 0.93 [0.76 [0.76–1.13], respectively). After stratification for CAD, the association remained significant in women with CAD but not in men with CAD (0.60 [0.44–0.83] and 0.96 [0.76 [0.75–1.23], respectively.

Conclusion: The traditional cardiovascular risk-factors associated with future surgery for valvular heart disease and for surgery of the ascending aorta, however with a clear difference if there was concomitant CAD or not. Arterial hypertension was a major risk factor for surgery for AS in younger patients without CAD, whereas impaired fasting glucose (IFG) associated with surgery in elderly patients without CAD. High levels of Lp(a) and a high Apo B/A1 ratio were associated with future AVR only in patients with concomitant CAD. Similarly, early renal impairment expressed as low ratio of eGFR by cystatin C and by creatinine (“shrunken pore”) associated with future AVR.

Keywords
Valvular heart disease, aortic stenosis, bicuspid aortic valve, cardiovascular risk factors, hypertension, diabetes mellitus, smoking, hypercholesterolemia, obesity, shrunken pore, renal failure